Cost-effectiveness of Real Time Continuous Glucose Monitoring to Target Glucose Control in Preterm Infants

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Abstract

The optimal management of glucose levels in critical care remains an area for research due to the problems of balancing the risks of hyperglycemia versus hypoglycemia. This paper reports the first economic evaluation of real time continuous glucose monitoring to guide the clinical management of preterm infants, based on evidence from the REACT trial. Bivariate regression of costs (£, 2016-17 prices) and cases of adequate glucose control, with multiple imputation of missing data, was conducted. When the economic evaluation was restricted to the first week of life, real time continuous glucose monitoring was associated with increased costs and a statistically significant increase in adequate glucose control. When the assessment was performed over a time horizon extending to 36 weeks' corrected gestational age, real time CGM was dominant in health economic terms, i.e. associated with lower costs and better outcomes. These results largely remained robust to a range of sensitivity analyses and sub-group analyses designed to address uncertainty and heterogeneity surrounding the cost-effectiveness outcomes. This study suggests that the use of real time continuous glucose monitoring in preterm infants is associated with a high probability of cost-effectiveness.

Key words: Real time continuous glucose monitoring; preterm; neonatal care; economic evaluation; cost-effectiveness

Introduction

The optimal management of glucose levels in critical care remains an area for research enquiry due to the problems of balancing the risks of hyperglycemia versus hypoglycemia. This is a particular problem in neonatal intensive care, where high-energy nutritional requirements are needed to support growth, and variable insulin sensitivity makes infants at risk from both hyperglycemia and hypoglycemia. Both, along with extreme glucose variability, are common in these infants and have been associated with increased mortality and morbidity.[1,2] One of the challenges is monitoring the rapid fluctuations in glucose levels using only intermittent blood glucose sampling. Attempts to reduce risks associated with hyperglycemia have often resulted in increased risk of hypoglycemia.[3–5] Furthermore, the use of masked continuous glucose monitoring (CGM) has revealed clinically silent episodes of hypoglycemia in the newborn that are associated with worse developmental outcomes in early childhood.[6,7]

Hyperglycemia has been associated with acute problems of osmotic diuresis and metabolic acidosis, as well as with increased risks of intraventricular haemorrhage, patent ductus arteriosus (PDA)[8], retinopathy of prematurity (ROP), and necrotizing enterocolitis (NEC).[2,9-11] The developing brain is also vulnerable to rapid changes in glucose levels[12] and hypoglycemia has been associated with occipital temporal lesions.[11] Thus, early control of glucose levels may be an important modifiable risk factor for clinical outcomes in the extremely preterm infant.

Managing glucose control is currently dependent on repeated measures of blood glucose, but in the preterm infant it is important to minimize infant handling and to limit blood loss. This has resulted in a dependence on relatively infrequent intermittent blood sampling.[13] The use of real time CGM in these vulnerable preterm infants could allow earlier detection and potentially prevention of exposure to extreme glucose levels.

CGM has been used in adult[14] and paediatric intensive care[15] to optimize glucose control, and preliminary data suggest it is feasible in preterm infants, but this has not been formally

evaluated.[7,16,17] The REAl time Continuous glucose moniToring in neonatal intensive care (REACT) project represented the first attempt to formally evaluate the use of real time CGM to guide the clinical management of preterm infants.[18] In this paper, we report the first economic evaluation of real time CGM based on evidence from the REACT project.

Methods

Trial Background

REACT (ISRCTN: 12793535) was an international open label, parallel group, individually randomized controlled trial of 180 infants with birth weight ≤1200g, gestation ≤36 weeks + 6 days and aged ≤24 hours. Infants were recruited between July 2016 and January 2019 from 13 neonatal intensive care units (NICUs) in the UK, Spain and The Netherlands and were randomized on a 1:1 ratio to either real time CGM or glucose control monitored and managed according to local standard clinical practice using intermittently sampled blood glucose levels. The primary efficacy outcome was defined by the percentage of time sensor glucose (SG) levels that were in the target range of 2.6-10 mmol/L (46 to 180 mg/dl), compared between study arms. The study protocol covering the economic evaluation was approved in the UK by the Health Research Authority (IRAS ID 168042), Research Ethics Committee (Ref: 15/EE/0158) and the Medicines and Healthcare products Regulatory Agency (Ref: CI/2016/0011) as well as by all local regulatory boards. The trial was funded by the UK National Institute for Health Research Efficacy and Mechanisms Evaluation Program. Further details of the trial, its sampling procedures, and methodology and outcome measures are reported elsewhere.[18]

Overview of economic evaluation

The main goal of the health economic evaluation for the REACT RCT was to evaluate the comparative cost-effectiveness of the two interventions: CGM versus standard approach in infants ≤1200g and ≤24 hours of age. The economic analysis adopted a National Health Service (NHS) and personal social services (PSS) perspective, capturing services provided by health and local authorities, in accordance with National Institute for Health and Care

Excellence (NICE) methodological recommendations.[19] For the purposes of the economic evaluation, cost-effectiveness was primarily presented in terms of incremental cost per additional case of adequate glucose control during the first seven days of life for the trial participants. However, clinical data were prospectively collected until 36 weeks' corrected gestational age; as a result, the costs and secondary outcomes incurred until 36 weeks were also reflected in the cost-effectiveness analysis. Study participants were hospitalised in a NICU and the majority of participants were in hospital at the 36 week corrected gestational assessment. Costs and outcomes were not discounted to present values due to the short time horizon of the economic evaluation, extending to either seven days or 36 weeks' corrected gestational age.

Measurement of resource use and costs

Health economic data were collected on:

1. Resource use and costs associated with CGM (direct intervention costs)
2. Broader health service use during the 36 week follow-up period

All costs were presented in British pounds sterling and valued at 2016-17 prices. If necessary, costs were inflated or deflated to 2016-17 prices using the UK NHS Hospital and Community Health Services (HCHS) Pay and Price Inflation Index.[20]

Direct intervention costs

Direct intervention costs encompassed the costs associated with the application of the comparator interventions, that is, CGM with guideline against standard care. In the intervention arm, infants had glucose sensors inserted, Enlite™, which were linked to a MiniMed™ 640G system and calibrated with point of care BG levels. As a result, the costs of the intervention included the cost of the Enlite™ sensor (MiniMed™ system), the costs associated with fitting the device to infants (hospital staff time), the costs associated with removal of sensors, and the cost of point of care glucose for calibration. The lifetime cost of the Medtronic system was annuitized and then further adjusted to reflect the time use of the device over the trial period. However, in order to reflect clinical practice outside the confines of a RCT, the resource inputs associated with masked continuous glucose monitoring and

the use of associated devices were not costed in the control arm although the relevant resource inputs were prospectively measured. The resource use associated with the direct intervention costs was collected prospectively. Table 1 provides an outline of the types of direct intervention-related resource inputs that were measured, and the sources for the respective unit costs of each resource input.

Cost estimates for staff inputs associated with key clinical events, such as time associated with sensor insertion and removal, were based on expert clinical advice about the duration of each event and the unit cost values for staff inputs were obtained from the NHS Agenda for Change 2016/17 pay scales.[21] The total direct intervention cost for each participant was estimated by estimating the compound of the associated resource use input values multiplied by their respective unit cost values.

Measuring broader resource use

The different types of resource categories for broader healthcare costs and their respective sources of unit costs are presented in Table 2.

Broader resource use data were collected for each infant using data extraction sheets completed by research nurses in each clinical centre who extracted the relevant data directly from routine hospital systems and patient records, following the final follow-up assessments at 36 weeks' corrected gestational age. The case report forms (CRFs) recorded details of length of inpatient stays by intensity of care, investigations performed (e.g. ultrasound scans, MRIs, ECGs, CT scans, X-rays, cranial ultrasound scans, EEGs), medications, and procedures performed (e.g. lumbar punctures, ventricular taps, long lines, surgeries, and interventions for ROP treatment). They also captured information surrounding transfers between hospitals and modes of transport used for hospital transfers and at final hospital discharge. Furthermore, where applicable, they captured resource use in hospitals that infants were transferred to. Distances associated with transfers between hospitals were calculated using Google Maps.

Valuation of resource use

Unit cost data were mainly obtained using the Department of Health and Social Care's Reference Costs 2016-7 schedules.[22]

Costs for sensor insertion, sensor monitoring, and sensor removal were calculated by applying clinical advice on the time taken for each activity; their respective unit costs were extracted from the NHS Agenda for Change 2016/17 pay scales and applied to the duration of each activity. Costs of medications for infants were estimated based on the doses and frequencies reported on the CRF with medication costs obtained from the British National Formulary (BNF).[23] Costs of blood transfusion products such as platelets, red blood cells, and frozen plasma were obtained from NHS Blood and Transplant price list[24] and applied to the volume of use for each product.

When infants were transferred to another hospital, the distance between the study site and transferred location (miles) was calculated using Google maps and we applied fuel costs that were calculated using the Advisory Fuel Rates (AFR) obtained from UK government.[25] The fuel costs applied to the distances of hospital transfers in clinical sites located outside the UK were estimated in the same manner.

Measurement of outcomes

The primary clinical outcome measure for this study was the percentage of time SG readings fell in the target range of 2.6 - 10mmol/l (46 to 180 mg/dl), within the first seven days of life. Cost-effectiveness was primarily expressed in terms of incremental cost per additional case of adequate glucose control during the first seven days of life. For the primary cost-effectiveness analysis, adequate glucose control was defined a priori by the REACT clinical team as at least 80% of readings falling within the target range. However, in order to assess the robustness of the cost-effectiveness results, a number of sensitivity analyses were also performed that varied the threshold for number of readings falling within the target range of 2.6-10 mmol/l; hence, adequate glucose control was re-estimated at alternative thresholds of 60%, 70%, and 90% of readings falling within the target range with the alternative thresholds defined a priori. Given the nature of the outcome measure used in

this project and the methodological constraints surrounding utility measurement in newborn infants, cost-utility analysis using a preference-based measure such as quality-adjusted life years (QALYs) was not performed.

The secondary clinical outcome measures selected for secondary expressions of cost-effectiveness were NEC and bronchopulmonary disease (BPD) on the basis of animal and human evidence linking hyperglycemia with morbidity. Cost-effectiveness analyses using these secondary clinical outcome measures were also expressed using an incremental cost-effectiveness ratio (ICER) and expressed in terms of incremental cost per case of NEC averted, and incremental cost per case of BPD averted, using imputed costs for the entire period extending to 36 weeks' corrected gestation.

Cost-effectiveness analysis methods

Missing data

Missing data may be a particular issue for costs and the health outcome measures of interest and therefore it is required to deal with them in a standardised way. Within the health economic literature, RCTs have been criticised for failing to use appropriate methods to address missing data.[26]

Multiple imputation was adopted to impute missing data and avoid biases associated with complete case analysis. Multiple imputation was conducted based on Rubin's rule.[27] Multiple imputation was carried out on the main and secondary clinical outcome measures, using Markov chain Monte Carlo (MCMC) and predicted mean matching (PMM).[28] PMM is a semi-parametric imputation approach, and generally performs better than linear regression despite the similarities in method.[29]

It is recommended that potential predictors are incorporated into analytical models for multiple imputation.[29] Inclusion of explanatory variables enables the analyst to use multiple imputation by chained equations (MICE). In chained equations, missing values in variable X are replaced by draws from the posterior predictive distribution of X and imputation is repeatedly performed using the values of other independent variables.[30] Consequently, the multiple imputation models used baseline covariates (gestational age, gender, site,

randomisation arm), as well as health outcomes and cost components (glucose level, and costs associated with inpatient days, investigation, medical treatment, and surgical procedures).

For the CGM outcome, before implementing multiple imputation, linear interpolation using the known values of CGM before and after any missing values was firstly conducted given that the data followed a time series format.[31] Interpolation requires that the dependent variable be a function of independent variables, so glucose level was also interpolated for values of the time that glucose level was checked.[31,32] Then, likewise, the interpolated values were imputed using a chained equation with baseline covariates and costs. Five imputed datasets were generated as this has been considered to be sufficient to obtain valid results.[28]

Regression analysis

Generalised linear modelling (GLM) was used to estimate total costs and effectiveness. GLM is an estimation strategy well suited to modelling skewed data.[33] Exponentiation of the mean of the logs generates the geometric mean of the skewed dependent variable (in this case costs), which is a downward-biased estimate of the arithmetic mean.[34] In contrast, GLM predicts the mean of the log without using a smearing factor and thus tends to yield more consistent results. After conducting statistical tests such as the Pregibon link test and Pearson correlation test on cost data, the gamma family and log link function were chosen as an appropriate GLM form for the trial data.

By specifying the treatment group as an indicator within the GLM model, the incremental costs and outcomes attributable to CGM were estimated, whilst controlling for baseline covariates (treatment arm, study site, gestational age, gender, birth weight standard deviation score, whether the mother received antenatal steroids >24 hours prior to delivery, and whether the mother had diabetes during pregnancy).

Presentation of cost-effectiveness results

Summary statistics were estimated for resource use variables by treatment allocation and duration, either covering days one to seven, or the 36 week follow-up period. Between

treatment group differences in resource use and costs were initially compared using the two-sample t-test. Standard errors are reported for CGM and control group means. Mean differences are reported with 95% confidence intervals (CIs). Where there was evidence of non-normality in the continuous outcome measure, non-parametric bootstrapping, with 1000 samples, was used to estimate the effect of the intervention and bootstrapped 95% CIs for mean differences are reported. Cost-effectiveness was estimated using a bootstrap method to minimise sampling uncertainty. Nonparametric bootstrap methods generate multiple replications of the statistic of interest by sampling replications from the original data.[35,36] A total of 1000 bootstrap samples were drawn and incremental cost-effectiveness with associated 95% CIs were calculated. Estimates from each imputed dataset were used to run regressions using Rubin's rule.[35]

In order to express uncertainty around ICERs, and to show results across a range of cost-effectiveness thresholds, cost effectiveness acceptability curves (CEACs) were also generated on the basis of bootstrapped sample data.[37,38] These curves show the probability that CGM is cost-effective at different levels of the cost-effectiveness threshold based upon modelled variation in observed patient outcomes.[37]

To determine cost-effectiveness, CGM was compared to the standard approach on the basis of the cost per additional case of adequate glucose control. An alternative that is less effective and more costly, on average, than one (or a linear combination) of other alternatives is considered 'dominated' in health economic terms and therefore not considered when estimating ICERs. An alternative that is most effective (i.e. provides greatest additional adequate glucose control) and offers an ICER less than or equal to a benchmark value (the cost-effectiveness threshold) can be deemed 'cost-effective' compared to other alternatives.[39] However, there are currently no published cost-effectiveness thresholds for the primary and secondary clinical outcomes of the REACT trial. In addition, we searched the stated and revealed preference literature to identify any external evidence with respect to population preferences for health changes associated with adequate glucose control and for health changes associated with the secondary clinical

outcomes. No such preference values were revealed by our literature searches and hence ranges of hypothetical cost-effectiveness threshold values have been selected for our analyses. As a result, the net monetary benefit (NMB) of using CGM versus standard approach was also calculated across three pre-determined cost-effectiveness thresholds, namely £1,000, £5,000, and £10,000 per additional case of adequate glucose control.[39] Additionally, alternative cost-effectiveness threshold values were introduced for the secondary outcome analyses based on both the NEC and BPD outcomes (£10,000, £30,000 and £50,000 cost-effectiveness thresholds). A positive incremental NMB indicates that the CGM is cost-effective compared with the standard approach at the given cost-effectiveness threshold.

Sensitivity, sub-group and secondary outcomes analyses

Several sensitivity analyses were carried out to assess the robustness of the cost-effectiveness estimates. These were conducted under the following scenarios: (1) restricting the analyses to complete cases (i.e. those with complete cost and outcome data for the seven days or up to 36 weeks' corrected gestation); and (2) estimating incremental cost-effectiveness using different thresholds for adequate glucose control of 60%, 70%, and 90%. The same sensitivity analyses described above were repeated over alternative follow-up periods of the first seven days of life or extending to 36 weeks' corrected gestational age for the assessment of economic costs.

Two sets of pre-specified sub-group analyses were conducted to explore the heterogeneity in the cost-effectiveness results. Sub-group analysis was performed for each study site and for two gestational age groups: extremely preterm (<28 weeks) and very preterm (28 weeks to 32 weeks). A post-hoc sub group analysis was subsequently carried out using gender as an additional sub group category. All sub-group analyses were based on cases with imputed cost and outcomes data at seven days or 36 weeks' corrected gestational age. Cost-effectiveness outcomes were also re-estimated using the secondary outcomes of NEC and BPD.

Results

One hundred and eighty infants were randomized to ether real time CGM (n=85) or standard clinical practice (n=95). The REACT clinical results are reported in full elsewhere.[18]

Economic costs

Table 3 summarises the total NHS and PSS costs associated with resource use during days one to seven, day 8 to 36 weeks' corrected gestation, and the entire study period, for complete cases. The mean direct intervention costs were £11,198 for CGM compared with £9,934 for the standard approach over the first seven days; however, the mean unadjusted cost difference was not statistically significant at the 5% level. The cost of using the Enlite™ sensor and glucose monitoring was not counted for in the control arm, as it is not part of standard care. The total cost during the period covering day 8 to 36 gestational weeks was higher for the control arm, £61,065 versus £65,464, but this was not statistically significant at the 5% level. The main driver for the higher cost in the control arm during this period of follow up was the higher cost of neonatal care (mean length of stay in intensive care: 13.2 versus 16.7 days). Likewise, the mean total NHS and PSS cost throughout the entire follow-up period was higher for the control group (£75,348) than for CGM (£71,909); and the mean between-group cost difference was £3,439, but was not statistically significant at the 5% level.

Cost-effectiveness results

The cost-effectiveness results are presented in Table 4 and Table 5 for days one to seven, and the entire study period, respectively. The associated CEAC is graphically represented in Figure 1.

<u>Base case analysis</u>

Two base-case analyses were performed; firstly, imputed seven day intervention costs and cases of adequate glucose control as shown in Table 4 (with an 80% threshold selected for definition of adequate glucose control), and secondly, imputed costs and cases of

adequate glucose control (80% threshold) but with costs extending to 36 weeks' corrected gestational age and outcomes restricted to the intervention period (Table 5). For the first base-case analysis, trial participants in the CGM arm experienced a statistically significant increase in cases of adequate glucose control based on 1000 times bootstrap simulations (23% point increase in adequate glucose control) for the first seven day intervention period. Mean NHS and PSS costs (Table 4) were also lower in the control group (mean cost difference: £605). The ICER for the base-case analysis in Table 4 indicates that CGM is, on average, more costly and more effective. Assuming cost-effectiveness thresholds of £1,000, £5,000, and £10,000 per additional case of adequate glucose control, respectively, the probability of cost-effectiveness for CGM reaches 90% at approximately £6,000 whilst the NMB associated with CGM became positive at a cost-effectiveness threshold of £5,000.

For the second base case analysis in Table 5, the trial participants in the intervention arm experienced lower costs (mean cost difference: £2,877) and a 23% point increase in cases of adequate glucose control as before. CGM was not only less costly but also the more effective strategy in this second base case analysis and therefore dominant in health economic terms. To summarise, the base case analyses reported in Table 5 show that CGM is the dominant strategy in health economics terms.

Sensitivity analyses

The cost-effectiveness outcomes generated by the sensitivity analyses using different analytical scenarios (complete case, imputed costs with 60%, 70% and 90% thresholds selected for definitions of additional adequate glucose control) generally supported the base case findings. For the complete case analysis in Table 4, mean costs were higher in the CGM group (mean cost difference: £ 1,104, 95% CI: -38.56 to 2,247.11). The effectiveness results followed the same pattern as that for the base case analysis and showed that participants in the CGM experienced a statistically significant increase in proportion of glucose readings within the target range over the seven day intervention period (0.22; 95% CI: 0.05 to 0.4). For the four sets of sensitivity analyses in Table 4, the probabilities of cost-effectiveness of CGM reached approximately 90% at cost-effectiveness thresholds of

£10,000. Adopting 60% 70% and 90% thresholds for proportions of glucose readings within the target range, the costs for each group remained identical at £10,354 for the CGM group and £9,749 for the control group, whilst estimates of effectiveness varied. However, the pattern of increased effectiveness of CGM remained consistent across the scenarios using different levels of adequate glucose thresholds. The results presented in Table 5 support this finding. The notable difference is that CGM becomes the dominant strategy in health economic terms in the sensitivity analyses in Table 5 due to the lower costs of CGM compared with the standard approach. In brief, the sensitivity analyses generally support the findings of the base case analyses.

Sub-group analyses

Sub-group analyses were performed using the variables of: site, gestational age, and gender. For sites, a few study sites were dropped due to the insufficient numbers of observations in the study sites. In all the study sites presented in Table 4, effectiveness was greater for the CGM group than the standard approach and costs were also higher other than in site no N42 (Norwich). Sub-group analyses based on gestational age at birth and gender demonstrated the same pattern that costs and effectiveness were generally higher for CGM than standard care. Another notable finding was that costs were lower for males in the sub-group analyses.

Secondary outcome analyses

Using the two outcomes of NEC and BPD, secondary outcome analyses were performed. For these outcomes, increased effectiveness can be interpreted as reduced cases of NEC and BPD, and hence the denominator of the incremental cost-effectiveness ratio has been inverted. The secondary outcome analyses revealed that CGM averts more cases of BPD and NEC with higher costs than the standard approach when the assessment of economic costs was restricted to the seven day intervention period. Different cost-effectiveness threshold values were adopted for the secondary outcome analyses, namely £10,000, £30,000 and £50,000. In Table 5, the secondary outcomes revealed that the probability of cost effectiveness for CGM reached 80% at a £10,000 cost effectiveness

threshold. In the secondary analyses reported in Table 4, mean costs were higher in the CGM group (mean cost difference: £605, 95% CI: -379 to 1589). When both costs and outcomes were valued over a time horizon extending to 36 weeks' corrected gestational age (Table 5), estimates of effectiveness followed the same pattern as the base case analysis but the costs were lower for CGM (mean cost difference: £-2,877, 95% CI: -10,026 to 4,272), making CGM dominant in health economic terms.

Discussion

This paper reports the first economic evaluation of real time CGM in neonatal intensive care. The study revealed that when the assessment was restricted to the first week of life, real time CGM was associated with increased costs and a statistically significant increase in adequate glucose control. When the assessment was performed over the extended time horizon that mirrored the time horizon of the trial, real time CGM was dominant in health economic terms. These results largely remained robust to a range of sensitivity analyses and sub-group analyses designed to address uncertainty and heterogeneity surrounding the cost-effectiveness outcomes and, separately, when the secondary clinical outcomes of cases of BPD and NEC averted were considered.

Previous economic evaluations of real time CGM were conducted in clinical contexts outside of neonatal intensive care and therefore, a comparative assessment of cost-effectiveness evidence is not possible.[40-42] Moreover, prior to REACT, previous studies of real time CGM in infants had been restricted to a small number of extremely preterm infants.[9,43] Our data should, therefore, be of relevance to clinical decision-makers and service planners tasked with preventing the adverse sequelae of hyperglycemia, hypoglycemia, and glycaemic instability in preterm infants.

The economic evaluation reported in this paper was conducted according to nationally agreed design and reporting guidelines.[19,44] It was based on a randomised, multi-centre, controlled trial that avoided many of the selection biases that characterise observational studies and that provided a vehicle for comprehensive prospective assessments of resource

use and clinical outcomes. The study's cost accounting was rigorous and included all significant resource items calculated from a NHS and PSS perspective. A comprehensive analytical strategy was pursued to handle sampling uncertainty surrounding the baseline ICERs, methodological uncertainty surrounding design features of the economic evaluation, and decision uncertainty surrounding the value of the cost-effectiveness threshold. Readers should, however, consider caveats when interpreting the study results. First, the time horizon for the economic evaluation was restricted to the time horizon of the trial, extending to 36 weeks' corrected gestational age. The effects of real-time CGM for targeting glucose control in neonates on longer-term economic costs and health consequences, including its potential preventive effects of the sequelae of NEC and BPD, remains a topic for future research. This includes the requirement to develop a decision-analytic model as a basis for estimating long-term cost-effectiveness. Second, and in parallel, by adopting the recommended NHS and PSS perspective,[19] the economic evaluation excluded broader costs, such as costs borne by family members and informal carers. It is likely that incorporation of these broader societal costs would improve the relative long-term cost-effectiveness of real time CGM if larger studies confirm that it reduces the risk of pathologies such as NEC and BPD that are predictive of poor neurodevelopmental outcomes. Third, the effectiveness of real time CGM has not been measured in terms of a preference-based outcome measure, such as the QALY, for which external cost-effectiveness threshold values are available and which may have been more useful for comparative purposes.[19] This had the effect that we had to rely on arbitrary cost-effectiveness threshold values for achieving an additional case of adequate glucose control. Preference elicitation techniques developed by economists, such as the willingness to pay approach and stated preference discrete choice experiment methods could, in principle, be used to estimate individual and population preferences for the clinical sequelae of real time CGM.[45]

In conclusion, this study suggests that the use of real time CGM in preterm infants is associated with a high probability of cost-effectiveness. Decision-makers should consider the likely economic impacts of its implementation in routine clinical practice.

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Competing interests

All authors state that they have no financial relationships or competing interests relevant to this article to declare.

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Table 1: Direct intervention-related resource inputs and sources of unit costs

Resource type	Resource use	Unit cost source
Medtronic™ 640G system and Enlite™ sensors	Cost of 640G system and Enlite™ sensors	Manufacturers
Enlite™ sensor insertion and set up of MiniMed™	Staff time	NHS agenda for change[20.21] & clinician's advice
Sensor Glucose Monitoring	Staff time	NHS agenda for change[20.21] & clinician's advice
Removal of sensor	Staff time	NHS agenda for change[20.21] & clinician's advice
Point of care (Nova StatStrip®)	Cost of Nova Biomed devices	Manufacturers

Table 2: Broader resource inputs and source of unit costs

Resource type	Resource use	Unit cost source
Length of stay by level of care (e.g. intensive care, special care)	Staff salaries, on-costs, equipment, consumables and revenue and capital overheads	NHS Reference Costs[22]
Medications	Cost of medications	British National Formulary (BNF)[23]
Investigations	Staff time to deliver the investigations, associated costs	NHS Reference Costs[22]
Medical (surgical) treatment	Staff time to deliver treatment, associated costs	NHS Reference Costs[22]
Blood transfusion products	Cost of blood transfusion products	NHS Blood and transplant price list[24]
Surgical procedures	Staff time to deliver the interventions, associated costs	NHS Reference Costs NHS agenda for change[21.22]
Mode of discharge	Mode and distance of transfer or discharge to home	UK government[25]

Table 3: Cost differences between trial arms by follow-up period and cost category; complete cases (£, 2016-17 prices)

Costs (Day 1 to day 7)	Intervention (N=71)	Control (N=83)	Total (N=154)	Mean difference	Parametric 95 % CI	P- value	Bootstrap 95% CI
	Mean (SE)	**Mean (SE)**	**Mean (SE)**				
Equipment	87 (2)	n/a	n/a	n/a	n/a	n/a	n/a
Monitoring	165 (6)	n/a	n/a	n/a	n/a	n/a	n/a
Point of care testing	6 (0.3)	5 (0.3)	5 (0.2)	1.4	(0.6, 2.2)	0.001	(0.6, 2.2)
Length of stay	8656 (97)	8534 (132)	8590 (84)	121	(-213, 455)	0.5	(-172, 482)
Medications	79 (2)	77 (1)	78 (1)	2.8	(-2.8, 5.3)	0.5	(-3.3, 4.9)
Investigation	571 (31)	630 (33)	603 (23)	-59	(-148, 31)	0.2	(-148, 32)
Blood transfusion products	2 (2)	35.7 (34)	20 (19)	-34	(-108, 39)	0.8	(-132, 2)
Medical treatment	92 (17)	106 (18)	100 (12)	-14	(-63, 35)	0.4	(-68, 35)
Surgical procedures	544 (57)	527 (62)	535 (43)	17	(-153, 186)	0.6	(-139,196)
Other procedures	2 (2)	36 (34)	20 (19)	-34	(-108, 39)	0.4	(-144, 3)
Total	**11199 (976)**	**9934 (184)**	**10517 (462)**	**1265**	**(68, 4168)**	**0.2**	**(-560, 3090)**
Costs (Day 8 to 36 weeks' corrected gestation)	**Intervention (N=71)**	**Control (N=82)**	**Total (N=153)**	**Mean difference**	**Parametric 95 % CI**	**P-value**	**Bootstrap 95% CI**
	Mean (SE)	**Mean (SE)**	**Mean (SE)**				
Length of stay	59901 (2296)	62807 (2059)	61458 (1533)	-2906	(-8983, 3170)	0.3	(-9020, 2400)
Medication - insulin only	0.3 (0.1)	0.2 (0.1)	0.2 (0.1)	0.1	(-0.1, 0.4)	0.2	(-0.1, 0.4)
Investigation	677 (76)	841 (97)	765 (63)	-165	(-414, 84)	0.2	(-443, 53)
Blood transfusion products	222 (34)	279 (39)	252 (26)	-57	(-161, 47)	0.3	(-157, 52)
Medical treatment	244 (64)	531 (105)	398 (65)	-287	(-540, -35)	0.03	(-535, -65)
Surgical procedures	20 (14)	909 (837)	496 (449)	-889	(-2667,889)	0.3	(-3289, -21)
Other procedures	0 (0)	94 (62)	50 (33)	-94	(-225, 38)	0.2	(-244, -5)
Mode of transfers	2.8 (0.4)	3.6 (1)	3.2 (0.6)	-0.8	(-3.1, 1.4)	0.5	(-3.3, 0.8)
Total	**61065 (2376)**	**65464 (2381)**	**63423 (1690)**	**-4399**	**(-11080, 2283)**	**0.2**	**(-10713, 1773)**

Costs (Entire study period)	Intervention (N=69)	Control (N=81)	Total (N= 150)	Mean difference	Parametric 95% CI	P-value	Bootstrap 95% CI
	Mean (SE)	Mean (SE)	Mean (SE)				
Equipment	87 (2)	n/a	n/a	n/a	n/a	n/a	n/a
Monitoring	165 (6)	n/a	n/a	n/a	n/a	n/a	n/a
Point of care testing	5.8 (0.3)	4.5 (0.3)	5.1 (0.2)	1.3	(0.5, 2.1)	0.002	(0.6, 2.2)
Length of stay	68144 (2563)	71273 (2101)	69833 (1636)	-3129	(-9616, 3358)	0.3	(-9577, 3043)
Medications	79 (2)	78 (1)	78 (1)	-2.7	(-2.7, 5.5)	0.5	(-3, 5.5)
Investigation	1260 (94)	1471 (115)	1374 (76)	-212	(-513, 89)	0.2	(-505, 88)
Blood transfusion products	320 (49)	387 (53)	356 (36)	-67	(-211, 78)	0.4	(-203, 71)
Medical treatment	798 (99)	1062 (131)	941 (85)	-264	(-598, 70)	0.1	(-587, 45)
Surgical procedures	1047 (994)	939 (848)	989 (645)	109	(-2457, 2674)	0.9	(-2313, 3007)
Other procedures	2 (2)	131 (72)	72 (39)	-130	(-284, 25)	0.1	(-294, -7)
Mode of transfers	2.8 (0.4)	3.6 (1)	3.3 (0.6)	-0.8	(-3.1, 1.5)	0.5	(-3.2, 1)
Total	**71910 (2779)**	**75348 (2476)**	**73767 (1849)**	**-3439**	**(-10645, 2939)**	**0.4**	**(-10774, 3896)**

Table 4: Results of cost-effectiveness analyses (costs covering days 1 to 7) (£, 2016-17 prices)

Scenario	Treatment group, mean (SE) Cost		Incremental cost	Treatment group mean (SE)		Incremental effectiveness (95% CI)	ICER	Probability of cost-effectiveness			Net monetary benefits		
	CGM	Control		CGM	Control			P^a	P^b	P^c	NMB^a (95% CI)	NMB^b (95% CI)	NMB^c (95% CI)
Base case analysis													
Imputed costs and cases of adequate glucose control (80% threshold), covariate adjusted	10354 (597)	9749 (282)	605 (-379, 1589)	0.92 (0.05)	0.68 (0.05)	0.23 (0.07, 0.4)	2583	0.31	0.86	0.97	-276 (-308, -245)	718 (677, 759)	1961 (1899, 2023)
Sensitivity analyses													
Complete case attributable costs and cases of adequate glucose control (80% threshold)	11117 (743)	10013 (370)	1104 (-39, 2247)	0.93 (0.05)	0.7 (0.06)	0.22 (0.05, 0.4)	4923	0.08	0.56	0.89	-827 (-864, -790)	138 (90, 185)	1344 (1276, 1413)
Imputed costs and cases of adequate glucose control (90% threshold), covariate adjusted	10354 (597)	9749 (282)	605 (-379, 1589)	0.80 (0.1)	0.58 (0.06)	0.23 (-0.03, 0.48)	2670	0.33	0.81	0.93	-266 (-376, -157)	752 (581, 923)	2025 (1740, 2309)

Scenario	Treatment group, mean (SE) Cost		Incremental cost	Treatment group mean (SE)		Incremental effectiveness (95% CI)	ICER	Probability of cost-effectiveness			Net monetary benefits		
	CGM	Control		CGM	Control			P^a	P^b	P^c	NMB^a (95% CI)	NMB^b (95% CI)	NMB^c (95% CI)
Imputed costs and cases of adequate glucose control (70% threshold), covariate adjusted	10354 (597)	9749 (282)	605 (-379, 1589)	0.97 (0.04)	0.75 (0.05)	0.21 (0.06, 0.36)	2870	0.27	0.85	0.97	-292 (-396, -189)	621 (499, 742)	1762 (1590, 1935)
Imputed costs and cases of adequate glucose control (60% threshold), covariate adjusted	10354 (597)	9749 (282)	605 (-379, 1589)	0.97 (0.03)	0.83 (0.04)	0.14 (0.04, 0.25)	4223	0.26	0.65	0.90	-370 (-475, -265)	233 (114, 352)	987 (835, 1139)
Sub group analysis[d]													
Stratification by centre Cambridge N01	12542 (2275)	9873 (357)	2670 (-1819, 7158)	0.88 (0.06)	0.63 (0.1)	0.26 (0.03, 0.48)	10469	0.17	0.19	0.27	-2444 (-3015, -1874)	-2251 (-2821, -1681)	-2009 (-2582, -1437)
Stratification by centre Norwich N42	7770 (1163)	10297 (251)	-2527 (-4871, -182)	1	0.86 (0.12)	0.14 (-0.09, 0.37)	-17686	0.96	0.98	0.99	3666 (3345, 3987)	4087 (3753, 4420)	4612 (4251, 4973)

Scenario	Treatment group, mean (SE) Cost		Incremental cost	Treatment group mean (SE)		Incremental effectiveness (95% CI)	ICER	Probability of cost-effectiveness			Net monetary benefits		
	CGM	Control		CGM	Control			P[a]	P[b]	P[c]	NMB[a] (95% CI)	NMB[b] (95% CI)	NMB[c] (95% CI)
Stratification by centre Luton & Dunstable N43	10622 (182)	9309 (686)	1312 (-88, 2714)	0.91 (0.08)	0.69 (0.13)	0.22 (-0.06, 0.49)	6056	0.19	0.28	0.49	-982 (-1196, -768)	-495 (-704, -285)	114 (-108, 336)
Stratification by centre Wolverhampton N68	9592 (383)	9470 (788)	122 (-1517, 1760)	0.82 (0.12)	0.69 (0.15)	0.13 (-0.26, 0.51)	968	0.36	0.53	0.62	-317 (-498, -136)	21 (-192, 234)	444 (179, 708)
Stratification by centre Southampton N73	9181 (889)	8112 (546)	1069 (-1169, 3307)	1	0.83 (0.1)	0.17 (-0.04, 0.37)	6413	0.63	0.71	0.87	824 (291, 1357)	1582 (1128, 2036)	2529 (2100, 2958)
Stratification by centre Amsterdam ND3	10282 (535)	9290 (853)	992 (-848, 2832)	1 (0)	0.75 (0.17)	0.25 (-0.08, 0.58)	3967	0.40	0.56	0.72	-758 (-859, -658)	-462 (-583,-341)	-92 (-302, 118)
Stratification by gestational age at birth Extreme preterm (<28 weeks)	10035 (292)	10018 (254)	17 (-820, 854)	0.88 (0.06)	0.64 (0.06)	0.24 (0.08, 0.4)	71	0.69	0.99	1	221 (133, 310)	1191 (1067, 1315)	2403 (2212, 2594)
Stratification by gestational age at birth Very preterm (28 weeks to 32 weeks)	11531 (1724)	8937 (370)	2594 (-785, 5972)	0.93 (0.05)	0.79 (0.08)	0.14 (-0.05, 0.33)	18501	0.03	0.16	0.29	-2541 (-2886, -2196)	-1947 (-2305, -1589)	-1204 (-1601, -807)

Scenario	Treatment group, mean (SE) Cost		Incremental cost	Treatment group mean (SE)		Incremental effectiveness (95% CI)	ICER	Probability of cost-effectiveness			Net monetary benefits		
	CGM	Control		CGM	Control			P^a	P^b	P^c	NMB^a (95% CI)	NMB^b (95% CI)	NMB^c (95% CI)
Stratification by gender Male	9539 (331)	9735 (299)	-196 (-1041, 650)	0.91 (0.05)	0.60 (0.08)	0.31 (0.12, 0.5)	-632	0.88	1	1	498 (410, 585)	1734 (1608, 1859)	3278 (3074, 3483)
Stratification by gender Female	11666 (1595)	9517 (269)	2150 (-1037, 5336)	0.88 (0.06)	0.78 (0.07)	0.10 (-0.07, 0.27)	21496	0.08	0.22	0.27	-2077 (-2400, -1753)	-1678 (-2010, -1346)	-1179 (-1540, -819)
Secondary analysis													
	CGM	Control		CGM	Control			P^e	P^f	P^g	NMB^e (95% CI)	NMB^f (95% CI)	NMB^g (95% CI)
Imputed costs and cases of BPD averted, covariate adjusted	10354 (597)	9749 (282)	605 (-379, 1589)	0.66 (0.17)	0.52 (0.12)	0.14 (-0.28,0.56)	4286	0.65	0.73	0.74	962 (819,1105)	3936 (3531,4342)	6910 (6240,7580)
Imputed costs and cases of NEC averted, covariate adjusted	10354 (597)	9749 (282)	605 (-379, 1589)	0.87 (0.05)	0.71 (0.06)	0.16 (0, 0.33)	3697	0.82	0.95	0.97	1085 (885, 1285)	4296 (3781, 4812)	7508 (6662, 8354)

[a, b, c]Cost-effectiveness threshold set at £1,000, £5,000, and £10,000, respectively. [d]Subgroup analysis by site could not be performed for Oxford (N36), Surrey (N74), Barts (N85), Bristol (N86), Leeds (N87), Leicester (N88), or Barcelona (SP3) due to insufficient number of observations. [e, f, g]Cost-effectiveness threshold set at £10,000, £30,000, and £50,000, respectively

Table 5: Results of cost-effectiveness analyses over follow-up period extending to 36 weeks' corrected gestation (£, 2016-17 prices)

Scenario	Treatment group, mean (SE) Cost		Incremental cost	Treatment group mean (SE)		Incremental effectiveness (95% CI)	ICER	Probability of cost-effectiveness			Net monetary benefits		
	CGM	Control		CGM	Control			P^a	P^b	P^c	NMB^a (95% CI)	NMB^b (95% CI)	NMB^c (95% CI)
Base case analysis													
Imputed costs and cases of adequate glucose control (80% threshold), covariate adjusted	73505 (2758)	76382 (2258)	-2877 (-10026, 4272)	0.92 (0.05)	0.68 (0.05)	0.23 (0.07, 0.4)	-12273	0.8	0.86	0.92	3227 (3000, 3454)	4221 (3990, 4452)	5464 (5225, 5703)
Sensitivity analyses													
Complete case attributable costs and cases of adequate glucose control (80% threshold)	73200 (2480)	74773 (2237)	-1574 (-6557, 3410)	0.93 (0.05)	0.7 (0.06)	0.22 (0.05, 0.4)	-7016	0.07	0.62	0.91	1802 (1643,1961)	2768 (2602, 2933)	3974 (3797,4151)
Imputed costs and cases of adequate glucose control (90% threshold), covariate adjusted	73505 (2758)	76382 (2258)	-2877 (-10026, 4272)	0.8 (0.1)	0.58 (0.06)	0.23 (-0.03, 0.48)	-12687	0.81	0.86	0.91	3375 (2593, 4156)	4393 (3576, 5210)	5666 (4789, 6542)

Scenario	Treatment group, mean (SE) Cost		Incremental cost	Treatment group mean (SE)		Incremental effectiveness (95% CI)	ICER	Probability of cost-effectiveness			Net monetary benefits		
	CGM	Control		CGM	Control			P[a]	P[b]	P[c]	NMB[a] (95% CI)	NMB[b] (95% CI)	NMB[c] (95% CI)
Imputed costs and cases of adequate glucose control (70% threshold), covariate adjusted	73505 (2758)	76382 (2258)	-2877 (-10026, 4272)	0.97 (0.04)	0.75 (0.05)	0.21 (0.06, 0.36)	-13637	0.81	0.85	0.9	3348 (2572, 4124)	4262 (3476, 5047)	5403 (4599, 6207)
Imputed costs and cases of adequate glucose control (60% threshold), covariate adjusted	73505 (2758)	76382 (2258)	-2877 (-10026, 4272)	0.97 (0.03)	0.83 (0.04)	0.14 (0.04, 0.25)	-20066	0.81	0.83	0.89	3271 (2494, 4048)	3874 (3085, 4663)	4628 (3820, 5436)
Sub group analysis[d]													
Stratification by centre Cambridge N01	82336 (2895)	79688 (4287)	2648 (-7706, 13002)	0.88 (0.06)	0.63 (0.1)	0.26 (0.03, 0.48)	10385	0.3	0.38	0.56	-1997 (-3043, -951)	-963 (-2006, 81)	330 (-722, 1381)
Stratification by centre Norwich N42	63545 (19515)	73956 (4990)	-10411 (-48985, 28162)	1	0.86 (0.12)	0.14 (-0.09, 0.37)	-72879	0.79	0.79	0.82	12753 (8126, 17379)	13695 (9059, 18331)	14874 (10222, 19525)

Scenario	Treatment group, mean (SE) Cost		Incremental cost	Treatment group mean (SE)		Incremental effectiveness (95% CI)	ICER	Probability of cost-effectiveness			Net monetary benefits		
	CGM	Control		CGM	Control			P[a]	P[b]	P[c]	NMB[a] (95% CI)	NMB[b] (95% CI)	NMB[c] (95% CI)
Stratification by centre Luton & Dunstable N43	70091 (6103)	74115 (4544)	-4024 (-18633, 10586)	0.91 (0.08)	0.69 (0.13)	0.22 (-0.06, 0.49)	-18561	0.74	0.77	0.8	4385 (2910, 5860)	5208 (3714, 6701)	6236 (4708, 7764)
Stratification by centre Wolverhampton N68	79446 (6431)	88220 (5321)	-8774 (-25199, 7651)	0.82 (0.12)	0.69 (0.15)	0.13 (-0.26, 0.51)	-69708	0.79	0.8	0.81	7539 (5856, 9222)	7954 (6170, 9737)	8473 (6553,10392)
Stratification by centre Southampton N73	56614 (12085)	61969 (7603)	-5355 (-32051, 21341)	1	0.83 (0.1)	0.17 (-0.04, 0.37)	-32129	0.81	0.81	0.82	5994 (2283, 9705)	6904 (3220, 10589)	8043 (4386, 11700)
Stratification by centre Amsterdam ND3	72631 (16207)	75867 (8455)	-3236 (-38650, 32177)	1 (0)	0.75 (0.17)	0.25 (-0.08, 0.58)	-12945	0.67	0.68	0.71	4415 (162, 8669)	5810 (1521, 10099)	7553 (3212, 11893)
Stratification by gestational age at birth Extreme preterm (<28 weeks)	84532 (2548)	87024 (2423)	-2492 (-8872, 3888)	0.88 (0.06)	0.64 (0.06)	0.24 (0.08, 0.4)	-10443	0.81	0.88	0.91	2524 (1874, 3174)	3493 (2824, 4162)	4705 (4004, 5406)
Stratification by gestational age at birth Very preterm (28 weeks to 32 weeks)	59983 (3187)	57829 (2146)	2154 (-5541, 9849)	0.93 (0.05)	0.79 (0.08)	0.14 (-0.05, 0.33)	15365	0.37	0.4	0.45	-1506 (-2304, -707)	-911 (-1720, -102)	-169 (-1001, 664)

Scenario	Treatment group, mean (SE) Cost		Incremental cost	Treatment group mean (SE)		Incremental effectiveness (95% CI)	ICER	Probability of cost-effectiveness			Net monetary benefits		
	CGM	Control		CGM	Control			P^a	P^b	P^c	NMB^a (95% CI)	NMB^b (95% CI)	NMB^c (95% CI)
Stratification by gender Male	74004 (3800)	81783 (3860)	-7779 (-17801, 2243)	0.91 (0.05)	0.6 (0.08)	0.31 (0.12, 0.5)	-25123	0.93	0.96	0.99	7580 (6559, 8602)	8816 (7763, 9870)	10361 (9262, 11460)
Stratification by gender Female	72839 (3641)	71301 (2778)	1538 (-6991, 10067)	0.88 (0.06)	0.78 (0.07)	0.1 (-0.07, 0.27)	15381	0.33	0.35	0.37	-1732 (-2592, -872)	-1333 (-2200, -466)	-835 (-1717, 48)
Secondary analysis													
	CGM	Control		CGM	Control			P^e	P^f	P^g	NMB^e (95% CI)	NMB^f (95% CI)	NMB^g (95% CI)
Imputed costs and cases of BPD averted, covariate adjusted	73505 (2758)	76382 (2258)	-2877 (-10026, 4272)	0.66 (0.17)	0.52 (0.12)	0.14 (-0.28,0.56)	---20368	0.82	0.82	0.81	4466 (4167,4764)	7440 (6920,7959)	10414 (9645,11183)
Imputed costs and cases of NEC averted, covariate adjusted	73505 (2758)	76382 (2258)	-2877 (-10026, 4272)	0.87 (0.05)	0.71 (0.06)	0.16 (0, 0.33)	-17568	0.88	0.94	0.97	4726 (3923, 5529)	7937 (6986, 8888)	11149 (9971,12327)

[a, b, c]Cost-effectiveness threshold set at £1,000, £5,000, and £10,000, respectively. [d]Sub-group analysis by site could not be performed for Oxford (N36), Surrey (N74), Barts (N85), Bristol (N86), Leeds (N87), Leicester (N88), or Barcelona (SP3) due to insufficient number of observations. [e, f, g]Cost-effectiveness threshold set at £10,000, £30,000, and £50,000, respectively